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ORIGINAL RESEARCH

Chronic Disease Burden After Congenital Heart Surgery: A 47-Year Population-Based Study With 99% Follow-Up

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BACKGROUND: Postoperative morbidity is an increasingly important outcome measure of patients who have undergone congenital heart surgery (CHS). We examined late postoperative morbidity after CHS on the basis of patients' government-issued medical special reimbursement rights.

METHODS AND RESULTS: Between 1953 and 2009, 10 635 patients underwent CHS at <15 years of age in Finland. We excluded early deaths and mental disabilities. Noncyanotic and cyanotic defects were divided into simple and severe groups, respectively. We obtained 4 age-, sex-, birth time–, and hospital district–matched control subjects per patient. The Social Insurance Institution of Finland provided data on all medical special reimbursement rights granted between 1966 and 2012. Follow-up started at the first operation and ended at death, date of emigration, or December 31, 2012. A total of 8623 patients met inclusion criteria. Follow-up was 99.9%. A total of 3750 patients (43%) required special reimbursements rights for a chronic disease. Cardiovascular disease was the most common late morbidity among patients (28%), followed by obstructive pulmonary disease (9%), neurologic disease (3%), and psychiatric disease (2%). Heart failure (simple hazard ratio [HR], 56.3 [95% CI, 35.4–89.7]; severe HR, 918.0 [95% CI, 228.9–3681.7]) and arrhythmia (simple HR, 11.0 [95% CI, 7.1–17.0]; severe HR, 248.0 [95% CI, 61.3–1002.7]) were the most common cardiovascular morbidities. Hypertension was common among patients with coarctation of the aorta (13%; incidence risk ratio [RR], 8.9; 95% CI, 7.5–10.7). Psychiatric disease was more common among simple defects, particularly ventricular septal defects.

CONCLUSIONS: Chronic cardiac and noncardiac sequelae are common after CHS regardless of the severity of the defect, underscoring the importance of long-term follow-up of all patients after CHS.

Key Words: congenital heart disease ■ epidemiology ■ morbidity ■ outcome ■ pediatric cardiology

Congenital heart defects (CHDs) are the most common single-organ malformations, with a worldwide incidence of 9 to 13 of 1000 births annually.[1] In Finland, ≈1% of children are born with a CHD, of whom 60% require either surgical- or catheter-based correction or palliation. Previous register-based studies have established the improved operative mortality and late survival of this growing patient population.[2] The increasing number of patients surviving to adulthood, however, necessitates more focus on their morbidity and quality of life as measures of the quality of care and outcome. We previously established that, although overall survival has improved, patients remain at risk for premature death attributable to both cardiac-related and nonrelated causes, underlining the importance of long-term follow-up regardless of the severity of the defect.[3,4]

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CLINICAL PERSPECTIVE

What Is New?

- Cardiovascular and noncardiovascular morbidity is more common among patients after congenital heart surgery compared with the general population, regardless of defect severity.
- Polypharmacy is common among patients, regardless of the severity of the defect.
- Mental disorders are not uncommon among patients after congenital heart surgery, particularly among patients with simple defects.

What Are the Clinical Implications?

- Long-term follow-up is essential after congenital heart surgery for all defects, regardless of the severity of the defect.
- Follow-up in primary care is important to address the high incidence of noncardiovascular morbidity.
- More emphasis should be placed on mental health screening among adults with congenital heart disease, and mental health services should be made readily available for them.

Nonstandard Abbreviations and Acronyms

ASD	atrial septal defect
CHD	congenital heart defect
CHS	congenital heart surgery
COA	coarctation of the aorta
HLHS	hypoplastic left heart syndrome
PDA	patent ductus arteriosus
TGA	transposition of the great arteries
TOF	tetralogy of Fallot
UVH	univentricular heart
VSD	ventricular septal defect

In the current study, we combined data from 4 Finnish national registries to obtain a comprehensive profile of the postoperative morbidity of patients over a 5-decade time period in hopes of establishing the importance of postoperative follow-up of this patient group. Chronic morbidity was indirectly assessed by examining special reimbursement rights issued by the Finnish government to cover the cost of long-term medications for Finnish citizens.

METHODS

The Finnish Ministry of Social Affairs and Health granted permission for this study, and the ethical committee approved the research protocol. The data that support the findings of this study are available from the author Tommi Pätilä (tommi.patila@hus.fi) at Helsinki University Central Hospital upon reasonable request.

Patients and Data Collection

We obtained patient and operative data from the custom-built ProCardio version 8 (Research Registry of Pediatric Cardiac Surgery, Melba Group, Helsinki, Finland) database running on Filemaker Pro version 8.5 (Filemaker Inc, CA), which stores data on all pediatric congenital heart surgeries (CHSs) performed since 1953 in Finland at 5 university hospitals (Helsinki, Kuopio, Oulu, Tampere, and Turku) and 1 regional hospital (Aurora Hospital, Helsinki). Since 1997, all CHSs have been centralized to Helsinki University Central Hospital. We excluded patients who underwent closure of a patent ductus arteriosus (PDA) at an age of ≤30 days because of the high incidence of prematurity among this population. We also excluded isolated pacemaker implantations and patients with known mental disability. Only patients who survived their first operation were included (>30 days after the operation). Patient data were obtained from January 1966 to December 2009. The later starting point was chosen to coincide with the introduction of the medical special reimbursement program in Finland.

The Finnish Population Registry provided the status and time of death for all patients. The causes of death were gathered through autopsy reports and physician reports on a national scale. Statistics Finland supplied us with 4 age-, sex-, birth date–, and hospital district–matched control subjects per patient, along with causes of death for both patients and controls. Patients who were not included in the final analyses had their respective matched controls removed from the data. Informed consent from patients and the general population included in this study was waived because of the retrospective and anonymous nature of the investigation.

Every Finnish citizen is reimbursed for medications that treat chronic diseases. This reimbursement is granted by The Social Insurance Institution of Finland, which provides social security benefits to Finnish nationals. Morbidity was assessed by inspecting data on patients' medical special reimbursement entitlements obtained from The Social Insurance Institution of Finland. Once a patient is granted a special reimbursement right, he/she can purchase the medication required for his/her chronic condition and receive substantial subsidies from the government for it, so that the final out-of-pocket amount remains affordable for the patient. As such, the special reimbursement right does not represent a time point when a patient purchases a

certain medication, but rather the time when the patient is diagnosed with a disease that grants him/her a special reimbursement right. Thus, for the sake of statistical analyses, you can use the date a special reimbursement right is acquired as the date a patient is diagnosed with a disease.

The criteria for special reimbursement entitlements depend on the medication and require a signed letter of medical necessity from the patient's physician stating the indication of the drug. Each special reimbursement entitlement requires a specific attached *International Classification of Diseases* (*ICD*) diagnosis code. We obtained all special reimbursement entitlements and the associated *ICD-9* and *ICD-10* diagnoses between 1966 and 2012. Diagnoses were placed by both primary and specialty healthcare providers across the country.

Study Design

Diseases were grouped according to the indication of the special reimbursement entitlement, as presented in Table S1. Morbidity is presented as incidence of selected disease groups and compared between patients and controls by calculated rate and hazard ratios (HRs). We refrained from comparing time periods because of the heavy confounding effect from the change in special reimbursement policies throughout the years.

For the survival studies, follow-up ended at the date of the first special reimbursement entitlement within each disease group, death, emigration, or December 31, 2012. Each patient was assigned one primary diagnosis from a severity-based hierarchical list of cardiac defects: PDA, atrial septal defect (ASD), coarctation of the aorta (COA), ventricular septal defect (VSD), tetralogy of Fallot (TOF), transposition of the great arteries (TGA), hypoplastic left heart syndrome (HLHS), and univentricular heart (UVH). All remaining cardiac defects were collectively referred to as miscellaneous, including truncus arteriosus, atrioventricular canal, congenitally corrected TGA, pulmonary stenosis, total anomalous pulmonary venous return, partial anomalous pulmonary venous drainage, Ebstein anomaly, interrupted aortic arch, isolated valve defects, aortopulmonary window, vascular ring, trauma, pericardial disease, aortic aneurysms, and heart transplants. For patients with several cardiac defects, we chose the hierarchically more severe condition.[5,6] To simplify the analyses, we dichotomized defect severity into simple (PDA, ASD, COA, and VSD) and severe (TOF, TGA, HLHS, and UVH) defects, according to the lack or presence of cyanosis, respectively. Detailed operative data for select defects are presented in Table S2.

Statistical Analysis

Incidence risk ratios (RRs) were obtained using Poisson regression with 95% CIs and were based on incidence rates of first events. HRs were obtained using matching group stratified Cox regression models. The matching reference units were accounted for as strata in the Cox model. Survival data are presented in the form of Kaplan-Meier plots. We used the date the first special reimbursement right for each disease group was granted as the event of interest. Death and emigration were treated as censoring events, such that special reimbursements were treated as events of interest until the day of death or emigration. Two-tailed *P* values were obtained with the log-rank test. In the estimation of hazard rate curves, we used Poisson regression with splines to produce smoothed curves with a 95% confidence envelope. We used B-spline basis matrix for a natural cubic spline with knots at 5, 15, 25, 35, and 45 years. SDs are reported with mean values. Analyses were performed using R program with the Epi package (R Development Core Team, Vienna, Austria, 2011) and IBM SPSS Statistics version 25.0 (SPSS, Inc, Chicago, IL).

RESULTS

Patients

After excluding PDA operations at <30 days of life, we identified 10 635 patients who underwent CHS between 1953 and 2009. After excluding early deaths (<30 days after first operation), patients with known intellectual disabilities, and all patients who underwent CHS before 1966, 8631 patients remained. Eight patients were excluded because of insufficient data. Thus, follow-up coverage was practically 100% with 8623 patients (Figure 1). Mean length of follow-up to death or end of the study was 23 years (SD, ±12.1 years; Table 1). The mean age at the end of follow-up was 26.6 years (SD, ±14.2 years; Table 1) for all patients.

The sex ratio was equal among simple and miscellaneous defects but male dominant among severe defects (Table 1). Mean age at the first operation was 4.2 years among simple defects and 1.4 years among severe defects (Table 1). Of patients who survived their operation, 6% died during their subsequent follow-up (Table 1). The cause of death was defect related in 49% of cases in the simple group (133/270) and 87% of cases in the severe group (234/263) (Table 1). The most common defect-related cause of death was heart failure in both groups (44% simple and 36% severe; Table 1).

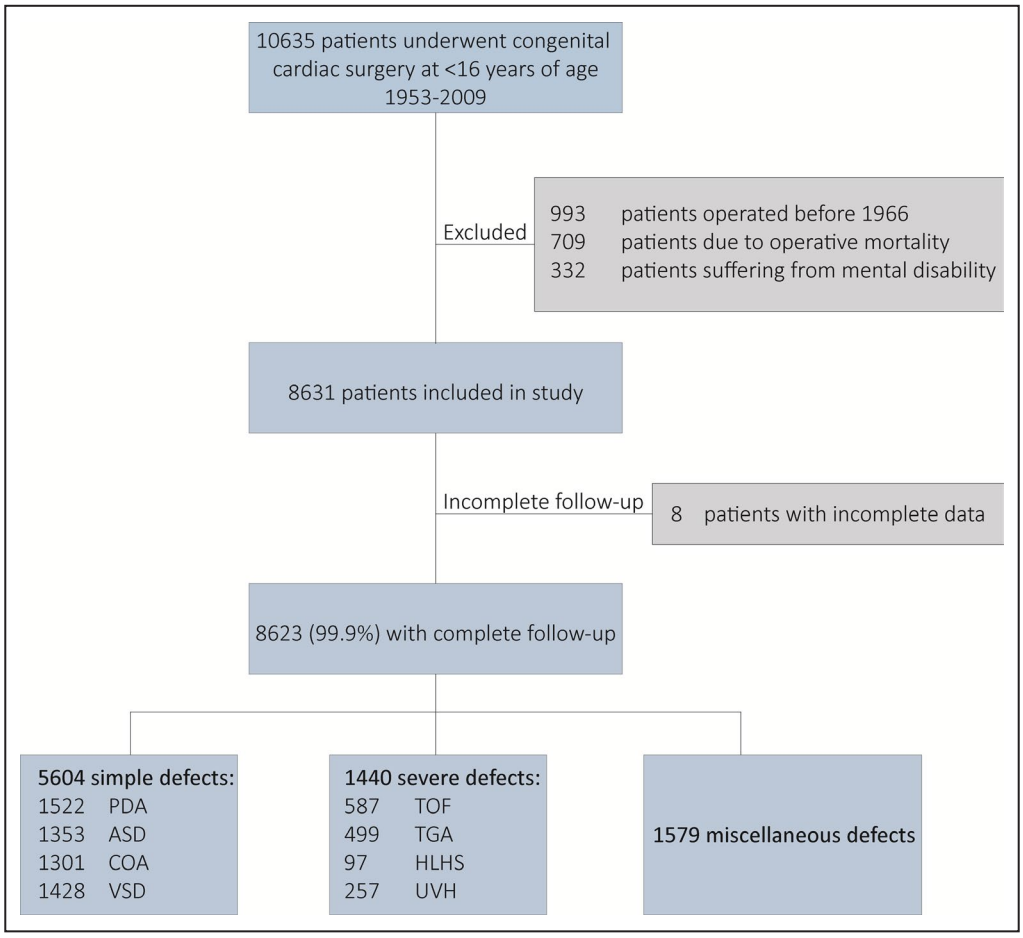

Figure 1. Flowchart of the study patient population.
ASD indicates atrial septal defect; COA, coarctation of the aorta; HLHS, hypoplastic left heart syndrome; PDA, patent ductus arteriosus; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; UVH, univentricular heart defect; and VSD, ventricular septal defect.

Chronic Morbidity and Need for Medications

A total of 3750 patients (43%) had a chronic disease with an entitlement to special reimbursements for their medication. Results of the most common special reimbursement groups are presented by defect severity in Figure 2 and by subgroups in Table 2. The absolute numbers of patients with special reimbursements are detailed in Table S3. Cardiovascular disease was the most common indication for special reimbursement rights among patients (RR, 11.5 versus controls; 95% CI, 10.5–12.7), followed by obstructive pulmonary disease (RR, 1.8 versus controls; 95% CI, 1.6–1.9), endocrine disease (RR, 2.0 versus controls; 95% CI, 1.7–2.2), neurologic disease (RR, 2.5 versus controls; 95% CI, 2.1–2.9), and psychiatric disease (RR, 1.3 versus controls; 95% CI, 1.1–1.6). Chronic diseases were on average more common in the severe group.

Cardiovascular Disease

One fourth (28%) of patients required special reimbursement rights for cardiovascular medications (18% of patients with simple defects and 53% of those with severe defects). Heart failure was the most common indication for cardiovascular medication across all defect groups (Figure 2, Table 2, and Table S3). Overall, patients with severe defects were at a higher risk of heart failure compared with those with simple defects (Figure 2 and Table 2). One fifth (20%) of patients required medication for heart failure (12% of patients with simple defects, 40% of patients with severe defects, and 32% of patients with miscellaneous defects) (Table S3). Patients with univentricular morphological UVH (67%) and HLHS (84%) required special reimbursement rights for heart failure medications most frequently, whereas patients with PDA and ASD were at lowest risk (Table 2). Freedom from medication for heart failure diminished

Table 1. Patient Characteristics

Characteristic	Defect Group		
	Simple	Severe	Miscellaneous
Defects, n (%)	5604 (100)	1440 (100)	1579 (100)
PDA	1522 (27)	…	…
ASD	1353 (24)	…	…
COA	1301 (23)	…	…
VSD	1428 (26)	…	…
TOF	…	587 (41)	…
TGA	…	499 (34)	…
HLHS	…	97 (7)	…
UVH	…	257 (18)	…
Miscellaneous	…	…	1579 (100)
Sex, n (%)			
Women	3065 (55)	547 (38)	752 (48)
Men	2539 (45)	893 (62)	827 (52)
Decade of first operation, n (%)			
1966–1969	489 (9)	69 (5)	54 (3)
1970–1979	1325 (23)	231 (16)	208 (13)
1980–1989	1378 (25)	334 (23)	346 (22)
1990–1999	1610 (29)	404 (28)	520 (33)
2000–2009	802 (14)	402 (28)	451 (29)
Age at first operation, mean±SD, y	4.2±4.0	1.4±2.7	3.5±4.4
<1 mo, n (%)	482 (7)	543 (38)	280 (18)
1–12 mo, n (%)	1335 (24)	462 (32)	494 (31)
1–4 y, n (%)	1335 (24)	267 (18)	275 (17)
>4 y, n (%)	2452 (44)	168 (12)	530 (34)
No. of operations, n (%)			
1	3955 (70)	754 (52)	…
2	1394 (25)	327 (23)	…
3	204 (4)	247 (17)	…
>3	49 (1)	110 (8)	…
Status, n (%)			
Alive	5241 (93)	1168 (81)	1565 (99)
Deceased	270 (5)	263 (18)	14 (1)
Defect related	133 (49)	234 (87)	4 (29)
Unknown	3 (2)	1 (0)	0
Reoperative	30 (23)	65 (28)	0
Cardiovascular	9 (7)	30 (13)	0
Sudden	33 (25)	54 (23)	3 (75)
Heart failure	58 (44)	84 (36)	1 (25)
Non–defect related	137 (51)	29 (13)	10 (71)
Unknown	93 (2)	9 (1)	0
Follow-up, mean±SD, y	25.0±12.0	18.3±11.9	20.6±11.2
Age at end of follow-up, mean±SD, y			
Alive	29.6±13.9	21.6±12.6	23.9±13.2
Deceased	21.8±17.2	11.5±12.7	43.2±6.9
All	29.1±14.1	19.7±13.2	24.1±13.3

ASD indicates atrial septal defect; COA, coarctation of the aorta; HLHS, hypoplastic left heart syndrome; PDA, patent ductus arteriosus; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; UVH, univentricular heart defect; and VSD, ventricular septal defect.

markedly during the first year after the first CHS, with 30-year survival rates of 60% (95% CI, 57%–63%) among severe defects and 95% (95% CI, 94%–95%) among simple defects (Figure 3A). The derivative of the survival curve (hazard rate curve) for heart failure medication was trimodal in the severe group, indicating a high need for heart failure medication immediately and an estimated 15 and 30 years after the first operation (Figure 3B). Furthermore, patients with TGA and UVH required medication for heart failure on average 6 years (SD, 8.1 years) and 2.5 years (SD, 5.1 years) after their first operation, respectively.

Hypertension was the second most common indication for cardiovascular medication after CHS (patients versus controls: RR, 2.8; 95% CI, 2.4–3.2). The postoperative need for special reimbursement rights to cover antihypertensives was highest after surgery for COA (13.0%), HLHS (6.2%), and UVH (3.1%). Patients with COA who required antihypertensives were on average older at their first operation compared with those without antihypertensives (6.0±4.9 versus 3.3±4.9 years, respectively; $P<0.0001$). Freedom from special reimbursement rights for antihypertensives at 30 years after the first operation was 95% (95% CI, 94%–96%) in the simple group and 97% (95% CI, 96%–98%) in the severe group (Figure 3A).

Of the patient population, 3% received special reimbursement for antiarrhythmics. Patients in all defect groups except PDA required special reimbursement rights for antiarrhythmics more frequently than the control population (all patients: RR, 25.7 versus controls; 95% CI, 18.6–45.0), with a higher incidence in the severe defect group. Among simple defects, patients with VSD had the highest RR for antiarrhythmics (Table 2), whereas univentricular defects had the highest risk among severe defects (HLHS, 8.2%; and UVH, 16.0%). The 30-year freedom from reimbursement rights for antiarrhythmics among severe defects was 87% (95% CI, 85%–90%; Figure 3A). The hazard rate curve for arrhythmia was trimodal in the severe group, with a peak of first special reimbursement rights within the first year and an estimated 15 to 20 and 25 to 30 years after the first operation (Figure 3B). Patients with ASD and COA required their first special reimbursement rights for antiarrhythmics an average of >20 years after their first operation, whereas patients with VSD, TOF, TGA, and UVH required them within an average of 11 to 18 years after their first operation.

Obstructive Pulmonary Disease

Obstructive pulmonary disease was the most common noncardiovascular indication for special reimbursement rights among patients (9%) and was more common among simple defects (490/5604; 9%; Table S3). Asthma was practically the only indication for special

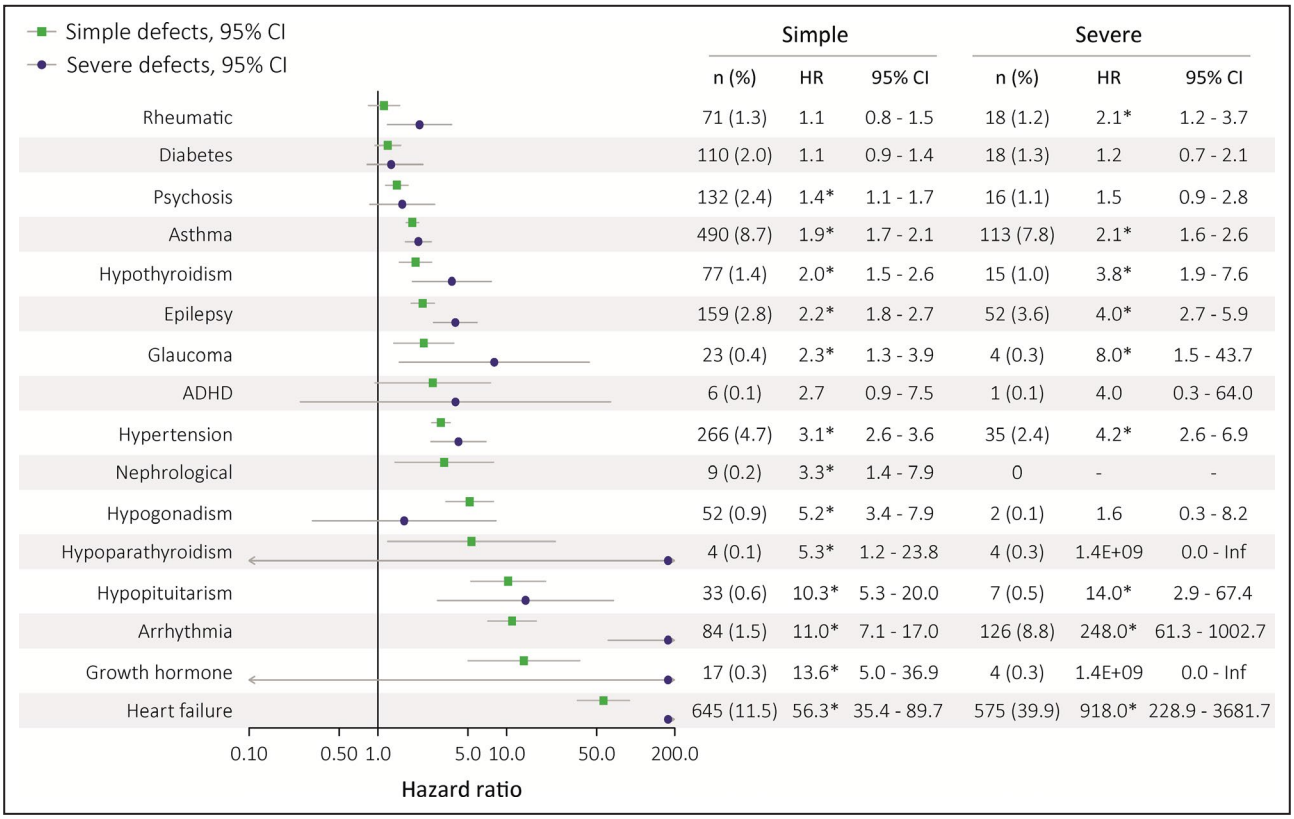

Figure 2. The hazard ratio (HR) of selected chronic diseases by defect severity compared with a matched reference population.
Results were obtained with a stratified Cox regression model comparing simple and severe patients with 4 sex-, age-, date of birth–, and hospital district–matched control subjects. Both the simple and severe defect groups were burdened with significantly more cardiovascular and noncardiovascular disease compared with the general population, including epilepsy, asthma, and endocrine disorders. *Denotes statistically significant results. ADHD indicates attention deficit hyperactivity disorder.

reimbursement rights for obstructive pulmonary disease and was significantly more common among patients compared with controls (RR, 1.8; 95% CI, 1.6–1.9 versus controls). Among simple defects, patients with VSD (8.8%) had the highest risk of asthma. Patients with HLHS had the highest risk, whereas patients with UVH had the highest absolute incidence of special reimbursement rights for asthma (8.9%) among severe defects. The 30-year freedom from special reimbursement rights for asthma was 91% (95% CI, 90%–92%) among simple defects and 91% (95% CI, 89%–92%) among severe defects (Figure 3A). The hazard rate was highest during the first 5 postoperative years (Figure 3B).

Endocrine Disease

All in all, 145 patients (1.7%) had a special reimbursement right for diabetes mellitus. Only patients with ASD had a higher risk for diabetes mellitus than the control population (Table 2). Patients with severe defects were at an increased risk of hypopituitarism (HR, 4.9; 95% CI, 3.4–7.2 versus controls), albeit with low absolute numbers (Table S3). There was also an increased risk for hypopituitarism among patients with ASD (Table S3).

Neurologic and Psychiatric Disease

Epilepsy was the most common neurologic indication for special reimbursement rights after CHS (Figure 2) and overall second most common noncardiovascular morbidity after CHS among all patients (Table S3). Patients with severe defects had a higher risk for requiring special reimbursement rights for epilepsy than those with simple defects (HR, 4.0; 95% CI, 2.7–5.9 versus controls), with 3.8% of patients with TGA, 3.5% of patients with UVH, and 8.2% of patients with HLHS requiring special reimbursement rights for antiepileptics. VSD had the highest risk of epilepsy among simple defects (Table 2).

This study does not include antidepressants because of the lack of a dedicated special reimbursement program. Regardless, patients with VSD required special reimbursement rights for psychiatric disease more often than the control population, particularly antipsychotics (Table 2). Patients with severe defects did not have a higher number of special reimbursements

Table 2. Incidence Rates and RRs of Selected Diseases by Defect Group, Obtained With a Poisson Regression Model With 95% CIs

Disease	Controls	PDA		ASD		COA		VSD		TOF		TGA		HLHS		UVH		Miscellaneous	
	Incidence/ 100 PY	Incidence/ 100 PY	RR (95% CI)	Incidence/ 100 PY	RR (95% CI)	Incidence/ 100 PY	RR (95% CI)	Incidence/ 100 PY	RR (95% CI)	Incidence/ 100 PY	RR (95% CI)	Incidence/ 100 PY	RR (95% CI)	Incidence/ 100 PY	RR (95% CI)	Incidence/ 100 PY	RR (95% CI)	Incidence/ 100 PY	RR (95% CI)
Nephrological	2.4	6.7	2.8 (0.8–9.5)	6.0	2.5 (0.6–10.8)	0.0	…	13.6	5.7 (1.9–16.7)*	0.0	…	0.0	…	0.0	…	0.0	…	3.1	1.3 (0.2–9.6)
Rheumatic	43.5	42.7	1.0 (0.6–1.6)	54.5	1.3 (0.8–2.0)	46.9	1.1 (0.6–1.8)	47.9	1.1 (0.6–1.9)	62.8	1.4 (0.7–2.9)	98.9	2.3 (1.2–4.4)*	0.0	…	27.9	0.6 (0.1–4.6)	74.4	1.7 (1.1–2.6)*
Psychiatric	71.3	90.1	1.3 (0.9–1.7)	99.9	1.4 (1.0–2.0)	84.8	1.2 (0.8–1.7)	144.3	2.0 (1.5–2.8)*	62.9	0.9 (0.4–1.8)	87.6	1.2 (0.6–2.5)	0.0	…	28.0	0.4 (0.1–2.8)	83.6	1.2 (0.8–1.7)
Alcohol or opioid addiction	1.5	2.2	1.5 (0.2–11.4)	3.0	2.0 (0.3–15.3)	3.1	2.1 (0.3–15.8)	6.8	4.5 (1.01–20.1)*	0.0	…	0.0	…	0.0	…	0.0	…	3.1	2.0 (0.3–15.7)
ADHD	1.8	2.2	1.3 (0.2–9.6)	3.0	1.7 (0.2–12.9)	3.1	1.8 (0.2–13.4)	10.2	5.8 (1.7–20.1)*	0.0	…	10.9	6.2 (0.8–47.0)	0.0	…	0.0	…	12.3	7.0 (2.3–21.2)*
Psychosis	68.3	85.6	1.3 (0.9–1.7)	93.8	1.4 (1.0–2.0)	78.5	1.2 (0.8–1.7)	130.6	1.9 (1.4–2.7)*	62.9	0.9 (0.5–1.9)	76.6	1.1 (0.5–2.4)	0.0	…	28.0	0.4 (0.1–2.9)	74.3	1.1 (0.7–1.6)
Neurological	55.5	81.4	1.5 (1.0–2.1)	125.4	2.3 (1.6–3.1)*	110.9	2.0 (1.4–2.8)*	145.9	2.6 (1.9–3.6)*	127.5	2.3 (1.4–3.8)*	213.9	3.9 (2.4–6.1)*	1128.8	20.4 (10.1–41.0)*	258.8	4.7 (2.4–9.0)*	193.3	3.5 (2.7–4.6)*
Epilepsy	49.0	67.7	1.4 (1.0–2.0)	116.1	2.4 (1.7–3.3)*	101.3	2.1 (1.4–3.0)*	145.9	3.0 (2.2–4.1)*	119.4	2.4 (1.5–4.1)*	213.9	4.4 (2.8–6.9)*	1128.8	23.1 (11.4–46.4)*	258.8	5.3 (2.7–10.2)*	193.3	3.9 (3.0–5.2)*
Other diseases	41.5	74.4	1.8 (1.3–2.6)*	66.9	1.6 (1.0–2.5)	72.1	1.7 (1.1–2.6)*	184.8	4.4 (3.3–5.9)*	248.5	6.0 (4.1–8.6)*	278.2	6.7 (4.5–10.1)*	12521.6	301.5 (222.7–408.1)*	1026.1	24.7 (17.4–35.2)*	388.1	9.3 (7.6–11.5)*
Glaucoma	6.3	22.4	3.6 (1.8–7.0)*	27.1	4.3 (2.1–8.8)*	6.2	1.0 (0.2–4.1)	3.4	0.5 (0.1–3.9)	7.8	1.2 (0.2–9.0)	32.9	5.2 (1.6–16.7)*	0.0	…	0.0	…	30.9	4.9 (2.5–9.7)*
Endocrine	107.6	157.0	1.5 (1.1–1.9)*	202.8	1.9 (1.5–2.4)*	206.2	1.9 (1.5–2.5)*	190.5	1.8 (1.3–2.3)*	191.1	1.8 (1.2–2.7)*	109.7	1.0 (0.5–1.9)	400.9	3.7 (1.2–11.6)*	346.3	3.2 (1.8–5.7)*	335.0	3.1 (2.5–3.8)*
Hypoparathyroidism	0.4	2.2	5.9 (0.6–56.8)	3.0	7.9 (0.8–76.4)	0.0	…	6.8	18.0 (3.0–107.9)*	7.8	20.7 (2.2–199.2)*	0.0	…	0.0	…	0.0	…	12.3	32.6 (7.3–145.6)*
Growth hormone	1.1	8.9	7.9 (2.4–25.6)*	6.0	5.3 (1.1–24.5)*	21.8	19.3 (7.2–51.7)*	13.6	12.0 (3.7–39.0)*	7.8	6.9 (0.9–54.3)	0.0	…	131.8	116.2 (14.7–917.0)*	56.2	49.5 (10.7–229.2)*	33.9	29.9 (12.4–72.2)*
Hypopituitarism	2.9	13.4	4.6 (1.9–11.4)*	30.1	10.4 (4.9–21.8)*	28.1	9.7 (4.5–21.0)*	20.5	7.1 (2.9–17.3)*	15.6	5.4 (1.3–22.9)*	10.9	3.8 (0.5–27.8)*	132.9	45.8 (6.2–339.3)*	84.5	29.1 (8.7–97.0)*	49.6	17.1 (9.0–32.4)*
Hypogonadism	14.4	26.9	3.7 (1.6–8.7)*	48.2	6.7 (3.2–14.0)*	197.7	27.5 (17.8–42.6)*	27.3	3.8 (1.4–10.5)*	0.0	…	0.0	…	0.0	…	112.3	15.6 (3.8–64.0)*	86.6	12.0 (6.7–21.6)*

(*Continued*)

Table 2. Continued

Disease	Controls	PDA		ASD		COA		VSD		TOF		TGA		HLHS		UVH		Miscellaneous	
	Incidence/ 100 PY	Incidence/ 100 PY	RR (95% CI)	Incidence/ 100 PY	RR (95% CI)	Incidence/ 100 PY	RR (95% CI)	Incidence/ 100 PY	RR (95% CI)	Incidence/ 100 PY	RR (95% CI)	Incidence/ 100 PY	RR (95% CI)	Incidence/ 100 PY	RR (95% CI)	Incidence/ 100 PY	RR (95% CI)	Incidence/ 100 PY	RR (95% CI)
Hypothyroidism	25.2	58.6	2.3 (1.5–3.5)*	39.3	1.6 (0.9–2.7)	21.8	0.9 (0.4–1.8)	82.4	3.3 (2.1–5.0)*	62.9	2.5 (1.2–5.1)*	32.8	1.3 (0.4–4.1)	132.0	5.2 (0.7–37.4)	84.5	3.4 (1.1–10.5)*	146.6	5.8 (4.2–8.0)*
Diabetes mellitus	66.8	69.6	1.0 (0.7–1.5)	118.3	1.8 (1.3–2.5)*	59.5	0.9 (0.6–1.4)	58.1	0.9 (0.5–1.4)	86.6	1.3 (0.7–2.4)	65.7	1.0 (0.4–2.2)	0.0	…	28.0	0.4 (0.1–3.0)	46.5	0.7 (0.4–1.2)
Obstructive pulmonary disease	210.1	330.8	1.6 (1.3–1.9)*	255.2	1.2 (1.0–1.5)	374.5	1.8 (1.5–2.2)*	425.9	2.0 (1.7–2.4)*	381.3	1.8 (1.4–2.4)*	408.3	1.9 (1.4–2.7)*	832.8	4.0 (1.8–8.8)*	676.5	3.2 (2.1–4.9)*	459.9	2.2 (1.8–2.6)*
Cardiovascular	75.5	146.1	1.9 (1.5–2.5)*	214.3	2.8 (2.2–3.7)*	846.3	11.2 (9.6–13.1)*	864.1	11.5 (9.7–13.5)*	1293.9	17.2 (14.2–20.8)*	2662.0	35.3 (29.5–42.2)*	91294.5	1210.1 (953.1–1536.3)*	15015.6	199.0 (166.8–237.5)*	1570.2	20.8 (18.3–23.7)*
Dyslipidemia	3.5	0.0	…	3.0	0.9 (0.1–6.3)	6.2	1.8 (0.4–7.4)	0.0	…	7.8	2.2 (0.3–16.3)	0.0	…	0.0	…	84.4	23.9 (7.3–78.6)*	3.1	0.9 (0.1–6.4)
Arrhythmia	5.0	11.2	2.2 (0.9–5.6)	75.8	15.0 (9.1–24.8)*	59.5	11.8 (6.8–20.4)*	96.4	19.1 (11.8–31.0)*	247.0	49.0 (30.6–78.3)*	514.7	102.1 (66.7–156.3)*	1143.7	226.8 (106.2–484.6)*	1269.0	251.7 (162.4–390.1)*	173.0	34.3 (22.8–51.6)*
Hypertension	61.6	88.0	1.4 (1.03–2.0)*	84.8	1.4 (0.9–2.0)	550.2	8.9 (7.5–10.7)*	89.4	1.5 (1.0–2.2)	78.6	1.3 (0.7–2.4)	99.1	1.6 (0.8–3.1)	807.9	13.1 (5.9–29.3)*	226.4	3.7 (1.8–7.4)*	140.8	2.3 (1.7–3.1)*
Heart failure	4.2	43.6	10.5 (6.0–18.4)*	53.4	12.8 (7.2–23.1)*	297.2	71.4 (47.8–106.6)*	673.2	161.8 (110.9–236.1)*	1041.4	250.3 (169.2–370.3)*	2288.6	550.1 (375.6–805.5)*	91294.5	21943.6 (14583.3–33018.7)*	12877.4	3095.2 (2121.9–4515.0)*	1320.7	317.4 (221.8–454.3)*

RRs were obtained by comparing the incidence of disease in each defect group with a sex-, age-, date of birth–, and hospital district–matched control population. ADHD indicates attention deficit hyperactivity disorder; ASD, atrial septal defect; COA, coarctation of the aorta; HLHS, hypoplastic left heart syndrome; PY, person years; PDA, patent ductus arteriosus; RR, incidence risk ratio; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; UVH, univentricular heart defect; and VSD, ventricular septal defect.

*$P<0.05$.

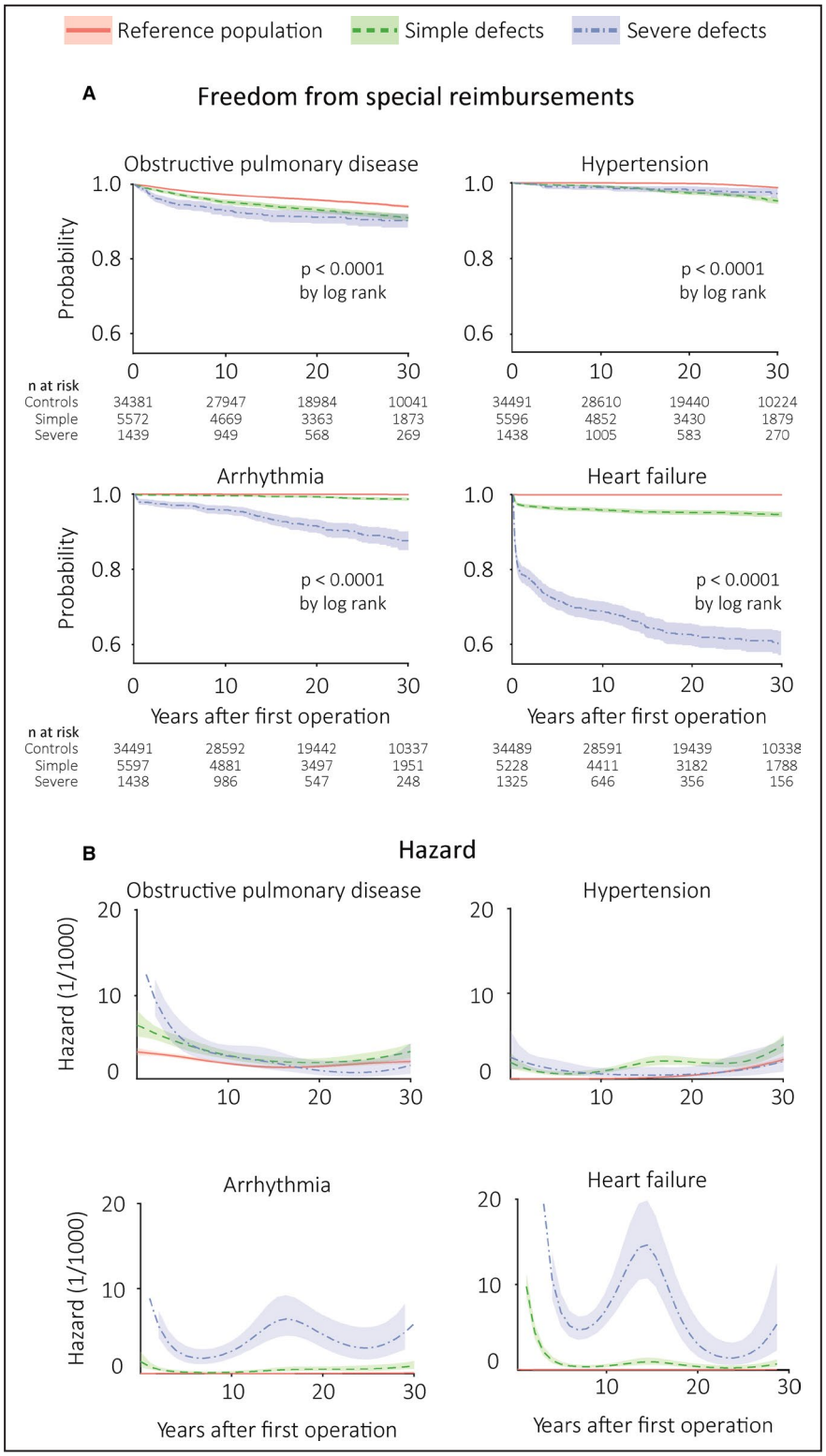

Figure 3. Freedom from selected chronic diseases and time-dependent hazard rates by defect severity.
A, Kaplan-Meier curves depicting survival free of special reimbursement rights for the 4 most common indications for long-term medications among patients. **B**, Hazard rate with 95% CI for the 4 most common disease groups among patients as a function of time. Hazard rates were obtained using Poisson regression model comparing the simple and severe groups with 4 sex-, age-, date of birth–, and hospital district–matched control subjects. Shaded areas represent 95% CIs.

for psychiatric medications compared with the control population.

Other Disease

Rheumatic disease was more common in the severe defect group compared with the control population (Figure 2). Patients were not at higher risk for hematological, dermatological, or inflammatory bowel disease. Malignancies were common among both patients and the general population, with patients with ASD having a higher incidence of cancer than their matched controls (data not shown).

Cardiovascular Morbidity by Defect Type and Operative Technique

Thirteen percent of all patients with COA who underwent an end-to-end operation and 10% who underwent the subclavian flap operation required special reimbursement rights for antihypertensives. Of all VSD patients, 28% required special reimbursement rights for heart failure (26% of patients with single VSD and 38% of patients with multiple VSDs). Of all TOF patients, 24% required special reimbursement rights for heart failure medications (37% of those who underwent staged correction versus 20% of those who underwent primary correction). In the TGA group, 24% of all patients who underwent an arterial switch operation (ASO) required special reimbursement rights for heart failure medication versus 56% for those who underwent the Mustard operation and 44% who underwent the Senning. Similarly, only 6% of ASO patients required special reimbursement rights for antiarrhythmics (14/250) versus 11% of Mustard (8/73) and 14% of Senning patients (17/122).

Cardiovascular Comorbidity

Almost one fifth of patients with UVH (19%) who required medication for heart failure required treatment for coexisting arrhythmia. Similarly, 17% of patients with TGA who had an entitlement for heart failure medication also had an entitlement to antiarrhythmic medications. From another point of view, 80% and 69% of patients with UVH and TGA, respectively, who required antiarrhythmics also had an entitlement to heart failure medication. Similarly, 50% of patients with TOF, 43% of patients with VSD, and 60% of patients with COA with antiarrhythmics required simultaneous treatment for heart failure.

All patients with UVH and 90% of patients with TGA who required antihypertensives were also entitled to medication for heart failure. Of patients with TOF who required antihypertensives, 45% were also entitled to medications for heart failure, with a corresponding 15% rate for patients with COA.

DISCUSSION

In this population-based study, we found that pediatric patients with CHD who underwent CHS were at significant risk for late morbidity regardless of the severity of their cardiac defect. The need for medication to treat cardiovascular disease was particularly pronounced.

Cardiovascular Morbidity

The higher prevalence of cardiovascular disease in the severe defect group was not surprising given the higher cardiac strain associated with more complicated defects, residual cardiac abnormalities, multiple operations, and complex and prolonged surgery.

Heart failure is a common late sequala among patients with CHDs and was by far the most common chronic morbidity for all cardiac defects.[7] A reported 40% to 50% of patients experience heart failure after the Fontan operation, representing the most common cause of death among this patient population.[4,8,9] In this study, the incidence of heart disease was proportional to the severity of the defect, with most (72%) of patients with single-ventricle physiological features requiring medication for heart failure. According to the literature, 40% to 50% of patients with TGA who undergo an atrial switch operation experience right ventricular failure late after surgery.[10] In our material, over a third of all TGA patients (36%) required heart failure medication, particularly patients who underwent an atrial switch operation (49%). The main reason is the abnormal cardiac physiological characteristics after the atrial switch operation. Patients with VSD are at risk for late aortic valve insufficiency, which may predispose to left ventricular strain if left untreated.[11] Also, pulmonary hypertension predisposes to heart failure, which could be the case among some patients with VSD operated on during the earlier decades. In our material, patients with VSD were at highest risk of heart failure (28%) among simple defects.

Arrhythmias were common in all defect groups, except PDA, the correction of which does not involve manipulation of the cardiac tissue. Interestingly, patients with COA had a higher than expected risk of arrhythmia, with no correlation with hypertension and operative age. The cause of postoperative arrhythmias is multifactorial and involves damage to the cardiac conduction system, tissue hypoxia, primary myocardial disease, and residual defects.[12] Arrhythmia and sudden deaths are recognized late complications after CHS, with >50% of all patients developing atrial arrhythmias before the age of 65 years and an overall increase in the cumulative risk with advanced age.[13] Previous studies have established the high incidence of arrhythmias in patients with TGA

who undergo atrial correction, with a corresponding low incidence among patients who undergo the ASO because of the lack of right atrial manipulation.[14,15] In the current study, we observed that a lower proportion of patients with TGA who underwent ASO required antiarrhythmics postoperatively versus those who underwent an atrial switch operation. These results reflect those from our previous study, where we found that the switch to using the ASO method was paralleled by a decrease in the incidence of sudden deaths compared with the Senning and Mustard techniques.[4] However, the shorter follow-up time of patients who underwent the ASO must be taken into account when interpreting these results. Patients with Fontan circulation have a reported 7% to 39% prevalence of postoperative arrhythmia.[16] In the current study, patients with single-ventricle defects had the highest need for antiarrhythmics, at a prevalence of 14%.

Patients with CHD are at risk of increased arterial stiffness.[17,18] Häcker et al[18] reported a significant correlation between low physical activity and increased arterial stiffness among this patient population, independent of the body mass composition. Moreover, studies have established a high prevalence of obesity among CHD patients, placing these patients at risk for metabolic syndrome.[19,20] Accordingly, we observed an increased risk of hypertension among patients with COA, PDA, and HLHS. Recurrent hypertension is a common late sequala after surgery for COA, with reports of a 30% to 75% postoperative prevalence.[21,22] In our material, 13% of patients required antihypertensives after correction of COA at an average of 24 years after their surgery.

Noncardiovascular Morbidity

Obstructive pulmonary disease was the most common noncardiovascular late morbidity after CHS in terms of absolute numbers. We strived to minimize the effect of prematurity on the results by excluding patients who underwent PDA ligation within the first month of life. Nevertheless, this method did not necessarily remove all patients who were born prematurely, which could potentially explain the higher incidence of obstructive airway disease among patients. Studies have suggested the coexistence of asthma among CHD patients, and possible misdiagnosis of pulmonary hypertension as asthma.[23–26] An alternative explanation for the higher prevalence of obstructive airway disease is misdiagnosis of cardiac asthma as reactive airway disease, higher incidence of mechanical ventilation, or low birth weight.

The risk for late neurological sequalae, particularly epilepsy, among the CHD population is well established.[27,28] In our material, epilepsy was the second most common noncardiovascular late complication after CHS, despite excluding mentally disabled patients. Neurological complications have been associated even with nonoperated CHD patients and have been connected to potential abnormal regulation of prenatal cerebral oxygen supply.[27] Also, de novo gene mutations may play a role in the neurodevelopmental outcome of these patients.[29]

Psychiatric disorders were more common among patients with simple defects, particularly VSD (3%), compared with the general population. Neuropsychological and mental health sequalae have been described after CHS, even among nonoperated patients.[30,31] In our material, we found no correlation between the prevalence of psychiatric disorders and suicides. However, our data did not include antidepressants, because the special reimbursement right for depression requires psychotic symptoms to be granted, thus leaving out an important psychiatric disorder from the scope of the study. Moreover, it is recognized that specifically syndromes characterized by a combination of cardiac defects, abnormal facial features, thymic hypoplasia, cleft palate, and hypocalcemia (CATCH 22) predisposes to psychosis later in life.[32] In the current study, however, we did not have data on the incidence of CATCH-22. Nevertheless, these results underscore the importance of screening for mental health disorders among both simple and severe defects.

Endocrine disorders were more common among the patient population. Hypogonadism and the need for growth hormone were particularly common among patients with COA. Coexisting congenital chromosomal defects and anomalies, such as Turner syndrome, can most likely explain most of these cases.

Finally, cancer is an increasingly recognized morbidity after CHS.[33] Our material revealed a higher incidence for the need of cancer medications among patients with ASD compared with the general population. However, chemotherapies are mostly administered in a hospital setting and not purchased by patients, which excludes them from our data. As such, the full scope of cancer incidence among patients and the general population remains unknown in our material.

LIMITATIONS

First, the current study did not include patients who only underwent catheter interventions. Second, information on special reimbursement entitlements, although informative, does not reflect the actual incidence and prevalence of disease, particularly if left undiagnosed or untreated. Third, this study does not

include medications that are not part of the special reimbursement program, such as antidepressants, antibiotics, and other relatively short-term medication regimens for commonly short-term curable diseases. Fourth, some medications that are administered in controlled hospital settings, such as cancer medications, were not included in this study. Thus, some diseases, particularly certain cancer types, may be underrepresented in the current data. Fifth, the special reimbursement data do not take into account the difference in practice among physicians, especially on the diagnosis used to apply for special reimbursement for a certain medication. This is particularly true for medications used for a multitude of indications, such as angiotensin-converting enzyme inhibitors and β blockers, which could be applied for special reimbursement under the diagnosis of hypertension or chronic heart failure. Sixth, some patient groups receive special reimbursement entitlements routinely postoperatively for certain cardiovascular medications, such as heart failure medication for single-ventricle morphological features, skewing the results. Seventh, several disorders may be treated nonpharmacologically, such as surgical comorbidity and disorders requiring psychotherapy or physical therapy. Finally, we have to acknowledge a possible selection bias and procedure bias because of the possibility of patients with CHDs having a higher probability of timely diagnosis and prescription of reimbursed medications because of their medical history and regular follow-up.

CONCLUSIONS

In conclusion, both cardiac and noncardiac chronic morbidity is common after pediatric CHS. More important, both simple and severe defects remain at significant risk for late morbidity, underscoring the importance of longitudinal follow-up in all patients after CHS.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Materials

Tables S1–S3

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SUPPLEMENTAL MATERIAL

Table S1. List of diseases with accepted special reimbursement entitlements in Finland categorized by disease group.

Cardiovascular
Atrial fibrillation
Chronic arrhythmia
Chronic heart failure
Clopidogrel
Coronary artery syndrome and associated dyslipidemia
Hypertension
Pulmonary hypertension
Dermatological
Generalized eryhtrodermia
Psoriasis
Severe dermatitis
Endocrine
Adrenal insufficiency
Diabetes insipidus
Diabetes type 2
Diabetes, insulin
Disorder in vitamin D metabolism
Dyslipidemia
Familial dyslipidemia
Growth hormone
Hypogonadism
Hypoparathyroidism

Hypopituitarism
Hypothyroidism
Osteoporosis
Primary or secondary hyperparathyreosis
Severe pancreatic deficiency
Gastrointestinal
Inflammatory bowel disease
Hematological
Aplastic anemia
Chronic coagulation disorders
Gammaglobulin deficiency
Isolated thrombocytopenia or granulocytopenia
Pernicious anemia / vB12 deficiency
Malignancies
Breast cancer
Cancer
Chronic myeloid leukemia or CLL
GIST, renal, or pancreatic cancer
Gynecological cancer
Hematologic cancer
Hematologic cancers
Hepatic, renal, or thyroid cancer
Melanoma and renal carcinoma
Non-small cell lung cancer and pancreatic cancer
Other malignancies

Prostate cancer
Renal, pancreatic, breast cancer or tuberous sclerosis-associated astrocytoma
Renal, pancreatic, or breast cancer
Metabolic
Obesity
Nephrological
Anemia related to chronic kidney failure
Chronic renal failure
Renal failure
Uremia requiring dialysis
Neurologic
Dementia (parkinson's or alzheimer)
Epilepsy
Epilepsy or other seizures
Multiple sclerosis
Myasthenia gravis
Narcolepsy
Parkinson's disease
Parkinsonism
Other
Anxiety related to mental disability
Congenital metabolic diseases
Cow milk protein allergy
Daily enteral feeding
Erectile dysfunction

Glaucoma
Hyperuricemia
Malabsorbance
Neuralgia
Secondary anemias (several)
Severe malnutrition
Psychiatric
ADHD
Alcohol or opioid addiction
Antipsychotic
Opioid addiction
Psychosis
Pulmonary
Chronic obstructive pulmonary disease
Rheumatic
Gout
Rheumatic disease
Sarcoidosis
Transplantation
Immunosuppressant
Medications status post-transplantation

Table S2. Surgical data on select defect groups.

Defect	1960s	1970s	1980s	1990s	2000s	All
COA, n (%)	96 (100)	346 (100)	330 (100)	305 (100)	224 (100)	1301 (100)
Operative technique						
End-to-end	91 (95)	297 (86)	235 (71)	218 (71)	186 (83)	1027 (79)
Subclavian flap	0 (0)	4 (1)	72 (22)	69 (23)	1 (0)	146 (11)
Other	5 (5)	33 (9)	13 (4)	4 (1)	6 (3)	61 (5)
Patch aortoplasty	0 (0)	10 (3)	5 (2)	2 (1)	11 (5)	28 (2)
Extended end-to-end	0 (0)	0 (0)	0 (0)	8 (3)	19 (9)	27 (2)
Unknown	0 (0)	2 (1)	4 (1)	3 (1)	0 (0)	9 (1)
Interposition graft	0 (0)	0 (0)	1 (0)	1 (0)	1 (0)	3 (0)
VSD, n (%)	60 (100)	215 (100)	348 (100)	499 (100)	306 (100)	1428 (100)
Defect type						
Single	58 (97)	196 (91)	304 (87)	402 (81)	263 (86)	1223 (86)
Multiple	1 (2)	9 (4)	32 (9)	66 (13)	36 (12)	144 (10)
Other	1 (2)	10 (5)	12 (3)	31 (6)	7 (2)	61 (4)
TOF, n (%)	47 (100)	107 (100)	142 (100)	155 (100)	136 (100)	587 (100)
Operative technique						
Primary	6 (13)	80 (75)	117 (82)	115 (74)	109 (80)	427 (73)
Staged	41 (87)	27 (25)	25 (18)	40 (26)	22 (16)	155 (26)
Other	0 (0)	0 (0)	0 (0)	0 (0)	5 (4)	5 (1)

	12		136	133	126	
TGA, n (%)	(100)	92 (100)	(100)	(100)	(100)	499 (100)
Defect type						
TGA, IVS	3 (25)	59 (64)	76 (56)	71 (53)	78 (62)	287 (58)
TGA, VSD	5 (42)	21 (23)	32 (24)	36 (27)	28 (22)	122 (24)
DORV, TGA type	0 (0)	2 (2)	16 (12)	14 (11)	13 (10)	45 (9)
TGA, VSD,						
LVOTO	3 (25)	2 (2)	5 (4)	8 (6)	2 (2)	20 (4)
Other	1 (8)	5 (6)	2 (1)	2 (1)	2 (2)	12 (1)
TGA, IVS,						
LVOTO	0 (0)	3 (3)	4 (3)	2 (2)	0 (0)	9 (2)
CCTGA	0 (0)	0 (0)	1 (0)	0 (0)	3 (2)	4 (1)
Operative technique						
ASO	0 (0)	0 (0)	18 (13)	115 (87)	117 (93)	250 (50)
Senning	0 (0)	12 (13)	105 (77)	5 (4)	0 (0)	122 (24)
Mustard	2 (17)	70 (76)	1 (1)	0 (0)	0 (0)	73 (15)
Other or unknown	8 (67)	6 (7)	5 (4)	3 (2)	7 (5)	29 (6)
Rastelli	2 (17)	4 (4)	7 (5)	10 (7)	2 (2)	25 (5)

COA, coarctation of the aorta; VSD, ventricular septal defect; TOF, tetralogy of Fallot; TGA, transposition of the great arteries; IVS, intact ventricular septum; DORV, double-outlet right ventricle; LVOTO, left ventricular outflow tract obstruction; CCTGA, congenitally corrected transposition of the great arteries.

Table S3. Number of patients with special reimbursement entitlements by defect severity and disease group.

	Simple, n (%)	Severe, n (%)	Miscellaneous, n (%)	All, n (%)
Metabolic	6 (0.1)	0 (0.0)	0 (0.0)	6 (0.1)
Hematological	5 (0.1)	2 (0.1)	3 (0.2)	10 (0.1)
Nephrological	9 (0.2)	0 (0.0)	1 (0.1)	11 (0.1)
Dermatologic	18 (0.3)	3 (0.2)	6 (0.4)	27 (0.3)
Gastrointestinal	37 (0.7)	4 (0.3)	7 (0.4)	48 (0.6)
Malignancies	46 (0.8)	2 (0.1)	10 (0.6)	58 (0.7)
Transplantation	13 (0.2)	23 (1.6)	27 (1.7)	63 (0.7)
Rheumatic	71 (1.3)	18 (1.2)	27 (1.7)	116 (1.3)
Sarcoidosis	3 (0.1)	0 (0.0)	0 (0.0)	3 (0.0)
Gout	2 (0.0)	2 (0.1)	2 (0.1)	6 (0.1)
Other rheumatic disease	66 (1.2)	16 (1.1)	25 (1.6)	107 (1.9)
Psychiatric	143 (2.5)	17 (1.2)	29 (1.8)	189 (2.2)
Alcohol or opioid addiction	5 (0.1)	0 (0.0)	1 (0.1)	6 (0.1)
ADHD	6 (0.1)	1 (0.1)	4 (0.3)	11 (0.1)
Psychosis	132 (2.4)	16 (1.1)	24 (1.5)	172 (2.0)
Neurological	173 (3.1)	53 (3.7)	65 (4.1)	291 (3.4)
Myasthenia gravis	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Other neurological	4 (0.1)	0 (0.0)	0 (0.0)	4 (0.0)
Multiple sclerosis	9 (0.2)	1 (0.1)	0 (0.0)	10 (0.1)
Epilepsy	159 (2.8)	52 (3.6)	65 (4.1)	276 (3.2)
Other diseases	202 (3.6)	152 (10.6)	169 (10.7)	523 (6.1)

Glaucoma	23 (0.4)	4 (0.3)	11 (0.7)	38 (0.4)
Anxiety related to mental illness	30 (0.5)	3 (0.2)	18 (1.1)	51 (0.6)
Other	149 (2.6)	145 (10.1)	140 (8.9)	434 (5.0)
Endocrine	314 (5.6)	52 (3.6)	127 (8.0)	493 (5.7)
Diabetes type 2	2 (0.0)	0 (0.0)	1 (0.1)	3 (0.0)
Hypoparathyroidism	4 (0.1)	4 (0.3)	4 (0.3)	12 (0.1)
Other endocrine	19 (0.3)	2 (0.1)	8 (0.5)	29 (0.3)
Growth hormone	17 (0.3)	4 (0.3)	13 (0.8)	34 (0.4)
Hypopituitarism	33 (0.6)	7 (0.5)	21 (1.3)	61 (0.7)
Hypogonadism	52 (0.9)	2 (0.1)	14 (0.9)	68 (0.8)
Hypothyroidism	77 (1.4)	15 (1.0)	49 (3.1)	141 (1.6)
Insulin-treated diabetes	110 (2.0)	18 (1.3)	17 (1.1)	145 (1.7)
Obstructive pulmonary disease	490 (8.7)	113 (7.8)	160 (10.1)	763 (8.8)
Cardiovascular	1008 (18.0)	758 (52.6)	632 (40.0)	2398 (27.8)
Other cardiovascular	1 (0.0)	3 (0.2)	1 (0.1)	5 (0.1)
Dyslipidemia	3 (0.1)	4 (0.3)	1 (0.1)	8 (0.1)
Coronary artery syndrome	9 (0.2)	15 (1.0)	9 (0.6)	33 (0.4)
Arrhythmia	84 (1.5)	126 (8.8)	64 (4.1)	274 (3.2)
Hypertension	266 (4.7)	35 (2.4)	49 (3.1)	350 (4.1)
Heart failure	645 (11.5)	575 (39.9)	508 (32.2)	1728 (20.0)